

## **REMARKS**

Applicant respectfully requests that the above amendments be entered and that the application be reconsidered in view of the amendments and the reasons that follow.

### **The Status of the Claims**

Upon entry of the amendments, claims 12-17 and 19 are under currently pending for examination and claims 1-11, 18, and 20-31 are withdrawn from consideration.

### **The Amendments**

Claims 12 and 14 have been amended. Claim 12 has been amended to emphasize the role of the tryptanthrin compound in providing an enhanced immune response to an antigen and to clarify the nature of the antigen. Claim 14 has been amended to remove BCG from the Markush group.

Claims 13-17 and 19 depend directly or indirectly from Claim 12 and contain all the limitations of Claim 12.

Entry of the amendments is respectfully requested. No new matter is added by the amendments, which finds full support in the application as filed such as in original claim 1 and paragraphs 14 and 44.

### **The 16 October 2007 Interview**

The undersigned thanks Examiner Chong for the courtesy extended to him and Ms. Lorna Tanner during the personal interview conducted regarding this application on 16 October 2007. The interview summary provided by the Examiner accurately reflects the discussions held during the interview.

### **The Rejection under 35 U.S.C. §103(a)**

Claims 12-17 and 19 stand rejected under 35 U.S.C. §103(a) as being obvious in view of US 5,441,955 to Baker et al. The Office has asserted that Baker teaches a tryptanthrin compound

that is disclosed in the present application and that Baker also teaches the use of the tryptanthrin compound in combination with other small molecule therapeutic agents.

**A *prima facie* case of obviousness requires the cited reference(s) to include all the claim limitations (MPEP 2142).**

The Office has asserted that it would have been *prima facie* obvious to combine the tryptanthrin compound (No. 1001) disclosed in both Baker and the present application with an adjuvant. Applicant respectfully traverses this rejection as the pending claims require an antigen, so that the mere combination of tryptanthrin and an adjuvant is lacking an antigen and is therefore not sufficient to support a *prima facie* case of obviousness.

The Office has pointed out in its rejection that BCG (Bacillus Calmette-Guerin, a weakened tuberculosis mycobacteris) is used in a vaccine against tuberculosis. Applicant interprets the Office's argument as suggesting the allegation that since BCG is used in as an antigen in a vaccine against tuberculosis and since the tryptanthrin compounds disclosed in Baker have anti-tuberculosis activity, one of skill in the art would be motivated to combine the BCG antigen with the tryptanthrin compounds to form a composition since they are used for the same purpose. In view of the amendments and the remarks submitted herein, withdrawal of the rejection is respectfully requested.

The Office has also pointed out in its rejection that BCG is a known immunostimulatory agent. Applicant interprets the Office's argument as suggesting the allegation that the art teaches combination of tryptanthrin with BCG as a immunostimulatory agent, and that BCG, by virtue of having antigenic properties based on its past use as an antigen in a vaccine for tuberculosis, properly supports a *prima facie* case of obviousness by meeting all the claim elements including that of an antigen. In view of the amendments and the remarks submitted herein, withdrawal of the rejection is respectfully requested.

As supported by the accompanying declaration from the inventor Mr. Nicholas Valiante, the claimed tryptanthrin compounds have been found to have the unexpected and previously unknown properties of being able to stimulate production of the cytokine TNF-alpha. Since

TNF-alpha is known to be a critical component of the biological pathways involved in immunity, these compounds are now being claimed in immunogenic compositions as adjuvants that are present in an amount effective to provide an enhanced immune response *to an antigen*.<sup>1</sup> Thus the present application teaches the adjuvant role of the tryptanthrin compound in the claimed composition, and this role is underscored in the amendments to the claim.

Applicant has now amended 12 to include the limitation of an effective amount of a tryptanthrin compound to provide an enhanced response to the antigen and to clarify that the antigen is other than BCG. Claim 14 has also been amended to remove BCG. Since a *prima facie* case of obviousness requires the cited reference to include all the elements of a rejected claim, the rejections to the pending claims are now moot as Baker does not teach all the claim limitations. Thus the mere combination of tryptanthrin with BCG does not provide the claim limitation of an effective amount of a tryptanthrin compound to enhance an immune response to the non-BCG antigen nor the claim limitation of a non-BCG antigen.

**The art teaches away from the combination of tryptanthrin with BCG.**

Notwithstanding the amendments to the claims, Applicant wishes to state for the record that the art teaches away from combining tryptanthrin with BCG based on either BCG's known use as an immunostimulatory agent or as a vaccine antigen.

First, Baker teaches use of tryptanthrins for treating an *infectious* disease, namely tuberculosis. However, BCG in its capacity as an immunomodulatory or immunostimulatory agent is currently used for treating *proliferative* diseases, particularly bladder cancer.

Second, BCG is a weakened, attenuated form of the tuberculosis mycobacterium. To

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<sup>1</sup> Vaccines generally comprise two essential components, an immunological agent mimicking the disease agent (i.e. an antigen) and an adjuvant. Antigens, typically weakened, non-lethal forms of the disease causing agent, are present to provoke an immune response and initiate the formation of immune memory cells specific for the antigen. However, it is well known that merely vaccinating a subject with an antigen is not generally sufficient to lead to an immune response sufficient to generate prolonged immunity to the antigen and to the disease agent that it mimics. Instead the provoking of an effective response often requires the presence of an adjuvant that provides an additional immunostimulant signal alerting the immune system to mount a specific response to the antigen. Therefore adjuvants themselves do not target the disease agent. Instead adjuvants assist antigens in training the immune system to recognize future infections by a disease agent. In some cases the immunity persists long after the vaccination event and even long after the antigen and adjuvant have been cleared from the vaccinated subject.

combine both tryptanthrin and BCG (as an immunostimulatory agent) in a single co-formulation composition as is now claimed would not be desirable based on the teachings of Baker, as the tryptanthrin would be expected to competitively bind to BCG in addition to the tuberculosis mycobacteria that it was meant to inhibit, thereby reducing the effectiveness of tryptanthrin as a therapeutic anti-microbial agent (see for example the assay results disclosed in Baker).

Third, as to the argument that BCG (as a vaccine) is known be used in the *prevention* of tuberculosis and tryptanthrin is taught in *treating* tuberculosis, therapeutic agents are generally *not* combined with vaccine components to arrive at a combination vaccine/therapeutic agent composition as a *co-formulation*. Vaccines typically have a very specific and limited dosing schedule (both in the frequency and amount of dosing) that is distinct from the dosing schedule of therapeutic agents, and the mode of administration of vaccines is typically a subcutaneous injection whereas most therapeutic agents are administered intravenously or orally. As alluded to earlier, vaccines are administered prior to infection while therapeutic agents such as tryptanthrins would be administered after infection. Even if BCG were to be used as a therapeutic vaccine to treat tuberculosis (which it is not), the different dosing schedules and modes of administration would suggest that it would be more practical and convenient to administer the vaccine and the therapeutic agent separately rather than as a co-formulation. The art therefore teaches away from such a combined composition.

**The art does not teach the claimed composition.**

Prior to the disclosure of the immune potentiating characteristics of the tryptanthrin compounds in the present application, there has been no teaching in the art of the use the tryptanthrin compounds in an immunogenic composition to stimulate an immune response for establishing protective immunity against a disease. Only the uses of these compounds as direct inhibitory anti-microbial agents are reported for treating a subject already infected with a microbial disease.

Therefore one of skill in the art would only recognize the direct inhibitory properties of the tryptanthrin compounds and would not seek to employ these compounds in the claimed

immunogenic antigen/tryptanthrin composition as there would be no expectation that the tryptanthrin compounds would enhance the immune response to the antigen for generating immunity to the antigen as is now claimed.

Accordingly, withdraw of the rejections under 35 U.S.C. §103(a) is respectfully requested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

Respectfully submitted,

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